In vitro patterning of pluripotent stem cell-derived intestine recapitulates in vivo human development.

Journal: Development

Publication Year: 2017

Authors: Yu-Hwai Tsai, Roy Nattiv, Priya H Dedhia, Melinda S Nagy, Alana M Chin, Matthew Thomson, Ophir Klein, Jason Spence

PubMed link: 27927684

Funding Grants: Stem cell therapy for inflammatory bowel disease

Public Summary:
The intestine plays a central role in digestion, nutrient absorption and metabolism, with individual regions of the intestine having distinct functional roles. For example, the most proximal region of the small intestine, the duodenum, is associated with absorption of nutrients such as iron and folate, whereas the more distal ileum is responsible for recycling bile salts. How intestinal regional identity is established during development is a largely open question. Here, we identified several genes that are expressed in a region-specific manner in the developing human intestine, and using human embryonic stem cell derived intestinal organoids, we demonstrate that the time of exposure to active FGF and WNT signaling controls regional identity. When region-specific organoids were transplanted into immunocompromised mice, duodenum-like organoids and ileum-like organoids retained their regional identity, demonstrating that regional identity of organoids is stable after initial patterning occurs. This work provides insights into the mechanisms that control regional specification of the developing human intestine and provides new tools for basic and translational research.

Scientific Abstract:
The intestine plays a central role in digestion, nutrient absorption and metabolism, with individual regions of the intestine having distinct functional roles. For example, the most proximal region of the small intestine, the duodenum, is associated with absorption of micronutrients such as iron and folate, whereas the more distal ileum is responsible for recycling bile salts. Many examples of region-specific gene expression in the adult intestine are known, but how intestinal regional identity is established during development is a largely open question. Here, we identified several genes that are expressed in a region-specific manner in the developing human intestine, and using human embryonic stem cell derived intestinal organoids, we demonstrate that the time of exposure to active FGF and WNT signaling controls regional identity. Exposure to short durations of FGF4 and CHIR99021 (a GSK3beta inhibitor that stabilizes beta-CATENIN) resulted in organoids with gene expression patterns similar to developing human duodenum, whereas long durations of exposure resulted in organoids similar to ileum. When region-specific organoids were transplanted into immunocompromised mice, duodenum-like organoids and ileum-like organoids retained their regional identity, demonstrating that regional identity of organoids is stable after initial patterning occurs. This work provides insights into the mechanisms that control regional specification of the developing human intestine and provides new tools for basic and translational research.